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Maternal Neuroendocrine Serum Levels in Exclusively Breastfeeding Mothers

Alison M. Stuebe,[1,2] Samantha Meltzer-Brody,[3] Brenda Pearson,[3] Cort Pedersen,[3] and Karen Grewen[3]

Abstract

Background: Low milk supply is a common cause of early weaning, and supply issues are associated with dysregulation of thyroid function and prolactin. However, hormone levels compatible with successful breastfeeding are not well defined, limiting interpretation of clinical lab results. In this study we sought to quantify ranges for thyroid-stimulating hormone (TSH), free thyroxine (T4), total T4, and prolactin in a cohort of exclusively breastfeeding women.

Materials and Methods: Women planning to breastfeed were recruited in the third trimester of pregnancy. Maternal endocrine function was assessed before and after a breastfeeding session at 2 and 8 weeks postpartum. We used paired *t* tests to determine whether values changed from the 2- to 8-week visit.

Results: Of 52 study participants, 28 were exclusively breastfeeding, defined as only breastmilk feeds in the prior 7 days, at both the 2- and 8-week study visits. Endocrine function changed with time since delivery: the TSH level was higher, whereas total T4, free T4, and prolactin levels were lower, at the 8-week visit than at the 2-week visit (by paired *t* test, $p \leq 0.01$). We found a wide range of prolactin values at the 8-week visit, with a 5th percentile value of 9 ng/dL before feeding and 74 ng/dL at 10 minutes after feeding.

Conclusions: Neuroendocrine function changes during the first 8 weeks after birth, and a wide range of values is compatible with successful breastfeeding. Further studies are needed to define reference values in breastfeeding women.

Introduction

Breastfeeding is a major determinant of health outcomes for mothers and infants. For parous women, not breastfeeding is associated with an increased risk of diabetes, hypertension, heart disease, and breast and ovarian cancer.[1] For infants, not being breastfed is linked with acute conditions such as otitis media and gastroenteritis, as well as increased risks of obesity, type 1 diabetes, and sudden infant death syndrome.[2] Thus, all major medical organizations recommend 6 months of exclusive breastfeeding, followed by continued breastfeeding through the child's first birthday or longer, as mutually desired by mother and infant.[3]

Although a growing proportion of women initiate breastfeeding in the United States, only 18.8% achieve the recommended 6 months of exclusive breastfeeding.[4] Maternal report of low milk supply is one of the most common reasons for formula supplementation, cited by 51.7% of women who discontinue breastfeeding in the first month postpartum.[5] Low milk supply may reflect preglandular, grandular, or postglandular problems,[6] and evaluation requires assessment of maternal endocrine function, breast anatomy, and infant latch and feeding patterns.

Endocrine evaluation may include assessment of thyroid function and prolactin levels. Thyroid disorders have been associated with low milk supply,[7–10] and circulating triiodothyronine (T3) and thyroxine (T4) are correlated with milk production.[11] Cross-sectional studies have found differences in thyroid functioning between lactating and nonlactating women,[12] but normal ranges for maternal thyroid-stimulating hormone (TSH), T4, and free T4 in exclusively breastfeeding women are not defined. Prolactin stimulates milk synthesis, and a low prolactin level has been implicated in etiology of low milk supply, but data are limited. Most longitudinal

[1]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.
[2]Carolina Global Breastfeeding Institute, Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
[3]Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, North Carolina.
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studies of prolactin were performed more than 20 years ago using assays that are not currently in use.[13–15] Furthermore, although the ratio of postfeeding to basal prolactin has been proposed as an index of endocrine function, normal ranges for this parameter have not been defined. Evidence also suggests that normal values change with time postpartum. A recent longitudinal study of prolactin levels in mothers of term versus preterm infants found that basal and poststimulation levels of prolactin decrease over time for both groups, reflecting the transition from endocrine to autocrine control of milk synthesis.[16] Currently, there are no reference values for normal prolactin and thyroid hormone levels in lactating women, limiting interpretation of clinical measures in women experiencing breastfeeding difficulties.

To address this gap, we measured TSH, T4, free T4, and prolactin levels in a cohort of women who were breastfeeding exclusively at 2 and 8 weeks postpartum. We defined exclusive breastfeeding as the infant receiving only breastmilk for the 7 days prior to assessment to identify a cohort of women with sufficient milk production to meet the infant's needs. We hypothesized that ranges would differ from 2 to 8 weeks postpartum, reflecting both changes in steroid binding globulin and transition from endocrine to autocrine control of milk synthesis.

Materials and Methods

We performed a secondary analysis of women enrolled in a longitudinal study of maternal mood and infant feeding that has been described in detail elsewhere.[17] Women who planned to breastfeed were enrolled from February 2010 to 2011 during the third trimester of pregnancy. Mothers returned with their infants at 1–2 and 6–8 weeks after birth for an observed feeding session. We restricted the current analysis to women who were exclusively breastfeeding, defined as no formula or other supplementation in the prior 7 days, at both the 1–2- and 6–8-week visit because this population of women was producing enough milk to meet infant demand. Our definition of exclusive breastfeeding included infants who were fed at the breast or fed mother's expressed milk via a bottle during the week prior to the study visit.

Study visit procedure

Participants presented at the University of North Carolina at Chapel Hill Mother-Infant Biobehavioral Lab for the observed feeding sessions at 2 and 8 weeks postpartum. All lab visits occurred in the early afternoon, which coincides with the nadir for TSH levels.[18] An antecubital intravenous line was placed to allow collection of multiple blood draws during a feeding session. After a 10-minute habituation period and 10 minutes of baseline rest, a blood sample was obtained, and each woman was asked to feed her infant as she usually would. A second blood sample was obtained at minute 10 of feeding, and a third sample was obtained 10 minutes after feeding was completed.

Data collection

At enrollment during pregnancy, participants were assessed by a board-certified psychiatrist with extensive training in administration of structured research interviews (S.M.-B.) using the depression and anxiety disorder modules of the Structured Clinical Interview Non-Patient version.[19] Breastfeeding intensity was assessed at 2 and 8 weeks postpartum with a 1-week infant feeding recall and was defined as the percentage of all milk feedings that were breastmilk.[20] Mothers were asked to report how many times in the last day they had fed their infant breastmilk, formula, or other foods. If they had not fed the food in the past day, they were asked how many times they had fed the food in the past week. We excluded from our analysis dyads with any infant intake other than breastmilk in the 7 days prior to the study visit.

We assessed current mood at each visit using validated instruments for assessment of mood and anxiety: the Edinburgh Postnatal Depression Scale (EPDS)[21,22] and the State and Trait Anxiety Inventories (STAI) of Spielberger.[23] Participants also reported any medications that they were taking. We excluded from the current analysis women who were taking galactogogues.

Neuroendocrine hormone assessment

Each venous blood sample was collected into prechilled Vacutainer® tubes (BD, Franklin Lakes, NJ), immediately cold-centrifuged, aliquoted into prechilled cryotubes, and stored at $-80°C$ for later endocrine assays. We used commercial radioimmunoassays (MP Biomedicals, Orangeburg, NY) to measure TSH (recovery, 94%; inter-assay coefficient of variation [CV], 5.4%; intra-assay CV, 4.3%), T4 (recovery, 96%; inter-assay CV, 5.3%; intra-assay CV, 4.3%), free T4 (recovery, 93%; inter-assay CV, 7.4%; intra-assay CV, 3.8%), and prolactin (recovery, 103.1%; inter-assay CV, 8.2%; intra-assay CV, 4.8%).

Analysis

We calculated mean, standard deviation, median, and 5% and 95% values for TSH, free T4, total T4, and prolactin levels at both the 2- and 8-week visits. We similarly reported median, 5%, and 95% values for postfeeding to basal prolactin ratio. We further present spaghetti plots of prolactin trajectory for study participants at both the 2- and 8-week visits to illustrate the range of values seen in our study population (Fig. 1).

To determine whether thyroid function and prolactin levels changed from 2 to 8 weeks postpartum, we used paired *t* tests. We further used unpaired *t* tests, Wilcoxon rank-sum tests, or Spearman correlation, as appropriate, to determine whether maternal characteristics, including parity (nulliparous versus multiparous), age (less than median versus greater than or equal to median), and depression/anxiety history (ever versus never, determined by standardized clinical interview), higher anxiety symptoms (STAI state ≥ 34 [with 34 being the median for women of reproductive age]), or current antidepressant use, were associated with differences in hormone levels. The small number of women with EPDS scores above the minor depression threshold (>9) precluded comparisons on this basis ($n=4$ at 2 weeks, $n=2$ at 8 weeks). We used Pearson correlations to test whether duration of the lab visit feeding episode or number of feedings per day was associated with hormone levels.

Results

We recruited 52 women during the third trimester. Of these, 48 attended the 2-week postpartum visit, among whom 33 were exclusively breastfeeding at the breast. Of these 33

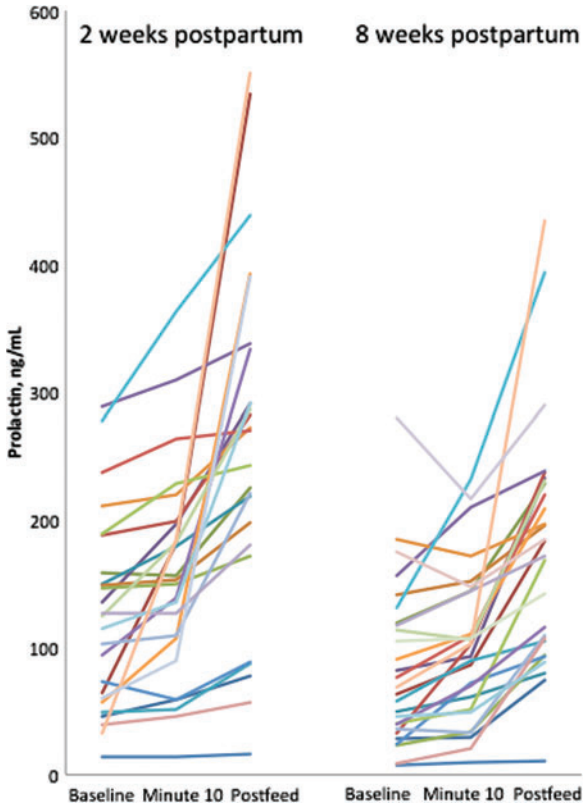

FIG. 1. Prolactin trajectories for 28 exclusively breastfeeding mothers at 2 and 8 weeks postpartum. Color images available online at www.liebertpub.com/bfm

women, 29 were still exclusively breastfeeding at the 8-week visit. One woman pumped during the study visits and was therefore excluded. The 28 women who were feeding their infants only breastmilk, either expressed or at the breast, in the preceding week and who fed at the breast at both study visits made up our sample.

Our study population was predominantly white, and the majority had completed college or postgraduate education (Table 1). By design of the parent study, almost half of the study participants had a history of depression or anxiety. At both visits, 10 women (35.7%) had scores on the STAI state inventory of ≥34. At 2 weeks postpartum, five women were taking antidepressants, of whom four had STAI state scores of ≥34 and one had an EPDS score of >9. At 8 weeks, six women were taking antidepressants, of whom five had STAI scores of ≥34 and two had EPDS scores of >9. All six women taking antidepressants had a current or lifetime history of anxiety or depression based on prenatally administered Structured Clinical Interview Non-Patient version. Of these six women, one was taking medication during pregnancy and at both postpartum visits, two initiated medication between the enrollment visit and the 2-week visit, and one initiated therapy between the 2- and 8-week visit.

Women presented for study visits at a median of 14 and 48 days postpartum. We found significant changes in observed neuroendocrine markers from the 2-week to the 8-week visit for all measured markers (Table 2). Free T4, total T4, and prolactin levels all declined within individual women between the 2- and 8-week visit (by paired *t* test, $p < 0.01$ for all comparisons), whereas the TSH level increased between the 2- and 8-week visit (by paired *t* test, $p = 0.004$). We found no association between parity, mood history, anxiety symptoms, maternal age, or current antidepressant use and TSH, T4, free T4, or prolactin values at any time point in our study sample (all $p > .05$).

Table 1. Study Population

Demographic	*Value*
Age (years) [mean (SD)]	32.1 (4.1)
Race [*n* (%)]	
White	26 (92.9)
Black or African American	2 (7.1)
Education [*n* (%)]	
<4-year college graduate	3 (10.7)
Graduated 4-year college	9 (32.1)
Postgraduate	16 (57.1)
BMI (kg/m^2) [*n* (%)]	
<25	9 (32.1)
25 to <30	11 (39.3)
≥30	8 (28.6)
Income [*n* (%)]	
Less than $40,000	4 (14.8)
$40,000–59,999	4 (14.8)
$60,000–99,999	8 (29.6)
$100,000 or above	11 (40.7)
Nulliparous [*n* (%)]	
No	13 (46.4)
Yes	15 (53.6)
Mode of delivery [*n* (%)]	
Spontaneous vaginal birth	20 (83.3)
Vacuum	2 (8.3)
Cesarean section	2 (8.3)
Depression or anxiety [*n* (%)]	
History	
Never	15 (53.6)
Lifetime, not current	8 (28.6)
Current	5 (17.9)
Taking antidepressants	
2 weeks postpartum	5 (17.9)
8 weeks postpartum	6 (21.4)
Higher anxiety[a]	
2 weeks postpartum	10 (35.7)
8 weeks postpartum	10 (35.7)

[a]State and Trait Anxiety Inventories state of ≥34, with 34 being the median for women of reproductive age.
BMI, body mass index; SD, standard deviation.

A wide range of prolactin trajectories was observed among exclusively breastfeeding women at study visits (Fig. 1 and Table 2). The 5th percentile for baseline prolactin among our 28 women was 32 ng/mL at 2 weeks and 9 ng/mL at 8 weeks. Ten minutes after feeding, the 5th percentile for prolactin was 57 ng/mL at 2 weeks and 74 ng/mL at 8 weeks. When we calculated the ratio of prolactin measured at 10 minutes after feeding to the prefeeding prolactin, the median was 1.50 (5–95%, 1.17–8.37) at 2 weeks and 2.31 (5–95%, 1.05–7.40) at 8 weeks. Postfeeding:prefeeding prolactin ratios were similar within women from the 2- to 8-week visit (by paired *t* test, $p = 0.61$).

The duration of the observed feeding varied among the participants in our study at both 2 weeks (median, 15 minutes; 95% confidence interval, 6–27) and 8 weeks (median, 13

Table 2. Neuroendocrine Markers at 2 and 8 Weeks Postpartum Among Exclusively Breastfeeding Mothers

	2 weeks	*8 weeks*	p[a]	*Reference*[b]
Days postpartum	13 (8–18)	48 (43–55)		
Breastfeedings per day	9 (8–12)	8 (6–11)	<0.001	
Observed feeding duration (minutes)	15 (6–27)	13 (6–25)	0.62	
TSH (mIU/L)				0.34–4.25
Baseline	0.90 (0.45–1.91)	1.19 (0.64–1.75)	0.004	
Free T4 (ng/dL)				0.7–1.24
Baseline	0.97 (0.79–1.32)	0.90 (0.67–1.18)	<0.001	
10 minutes after feeding	0.96 (0.78–1.19)	0.90 (0.66–1.13)	0.007	
Total T4 (μg/dL)				5.4–11.7
Baseline	9.02 (6.60–12.28)	6.42 (5.76–8.12)	<0.001	
10 minutes after feeding	9.15 (6.21–11.16)	6.49 (5.77–7.75)	<0.001	
Prolactin (ng/mL)				1.9–25
Baseline	124 (32–277)	68 (9–184)	<0.001	
Minute 10	153 (45–308)	102 (20–216)	<0.001	
10 minutes after feeding	270 (57–533)	177 (74–393)	<0.001	
Ratio 10 minutes after feeding: Baseline	1.50 (1.17–8.37)	2.31 (1.05–7.40)	0.61	

Data are median (5–95%) values.
[a]By paired *t* test, 2 versus 8 weeks.
[b]From Harrison's Online > Appendix: Laboratory Values of Clinical Importance (www.accessmedicine.com [accessed October 5, 2012]).
T4, thyroxine; TSH, thyroid-stimulating hormone.

minutes; 95% confidence interval, 6–25). At 2 weeks, we found a correlation between feeding duration and baseline TSH level (Pearson's $r=0.49$, $p=0.02$) and with prolactin levels 10 minutes after feeding (Pearson's $r=0.47$, $p=0.02$). We found no association between number of feedings per day and any endocrine measure at 2 weeks. At 8 weeks, feeding duration was correlated with prolactin levels 10 minutes after feeding ($r=0.46$, $p=0.02$). Prolactin physiology varied by number of feedings per day (Fig. 2). More frequent feedings were associated with higher baseline prolactin, although the correlation was not statistically significant ($p=0.12$) (Fig. 2A). Number of feedings per day was inversely associated with change in prolactin level from baseline to 10 minutes after feeding ($r=-0.57$, $p=0.002$) (Fig. 2D).

Discussion

In a sample of exclusively breastfeeding women, we found that both thyroid and prolactin values changed from 2 to 8 weeks postpartum. These results suggest that reference ranges specific for lactating women at discrete postpartum intervals may be needed to interpret endocrine assessment in the postpartum period. We further found that a wide range of prolactin values was compatible with exclusive breastfeeding and that the ratio of postfeeding:baseline prolactin levels varied with feeding frequency. These results provide a context in which to interpret thyroid and prolactin levels among women experiencing milk production difficulties.

Ours is the first study to our knowledge to report within-subject changes in thyroid physiology in breastfeeding women in the early postpartum period. Kurioka et al.[24] measured thyroid function during pregnancy and at 3–4 days postpartum and found lower free T4 and higher TSH than during pregnancy. Ekinci et al.[25] conducted a longitudinal study of thyroid function in each trimester and at 8–12 weeks postpartum and found that free T4 and free T3 levels decreased in the second and third trimester and were similar to first trimester values at 8–12 weeks postpartum, but the proportion of breastfeeding participants was not described. Iwatani et al.[12] measured thyroid function in a cross-sectional study of lactating and nonlactating woman at 3 months postpartum and nonpregnant controls and found that lactating women had lower free T4 and reverse T3 levels than nonlactating postpartum women as well as a higher thyroid-binding globulin level than nonpregnant controls. The authors concluded that thyroid hormone functioning is markedly different in lactating women. We found that total and free T4 values fall significantly from 2 to 8 weeks postpartum in breastfeeding women. These results may inform decisions regarding thyroid replacement dose in the early postpartum period.

Our work confirms and extends earlier work on normal ranges for prolactin during lactation. Several studies from the 1970s and 1980s measured prolactin levels over time, although these studies used assays no longer in clinical use. These authors reported a wide range of values associated with adequate milk production and further found that baseline and peak levels fall with time since birth, although the ratio of peak to baseline remained constant.[13–15]

The wide range of prolactin levels in our study and prior literature suggest that other factors, including lactocyte uptake of circulating prolactin,[26] may determine milk production. Indeed, Cox et al.[27] found no association between circulating prolactin and short-term milk synthesis rate or 24-hour milk production. These authors suggest that prolactin plays a permissive role in milk synthesis but that prolactin levels do not determine supply. If prolactin levels do not affect production, then agents such as domperidone and metoclopramide would not be expected to increase milk production among women with prolactin levels in the ''normal'' range. Given concerns about side effects from these agents,[28] future studies should explore whether baseline prolactin levels predict response to treatment.

We found that change in prolactin levels from baseline to 10 minutes after feeding was inversely correlated with

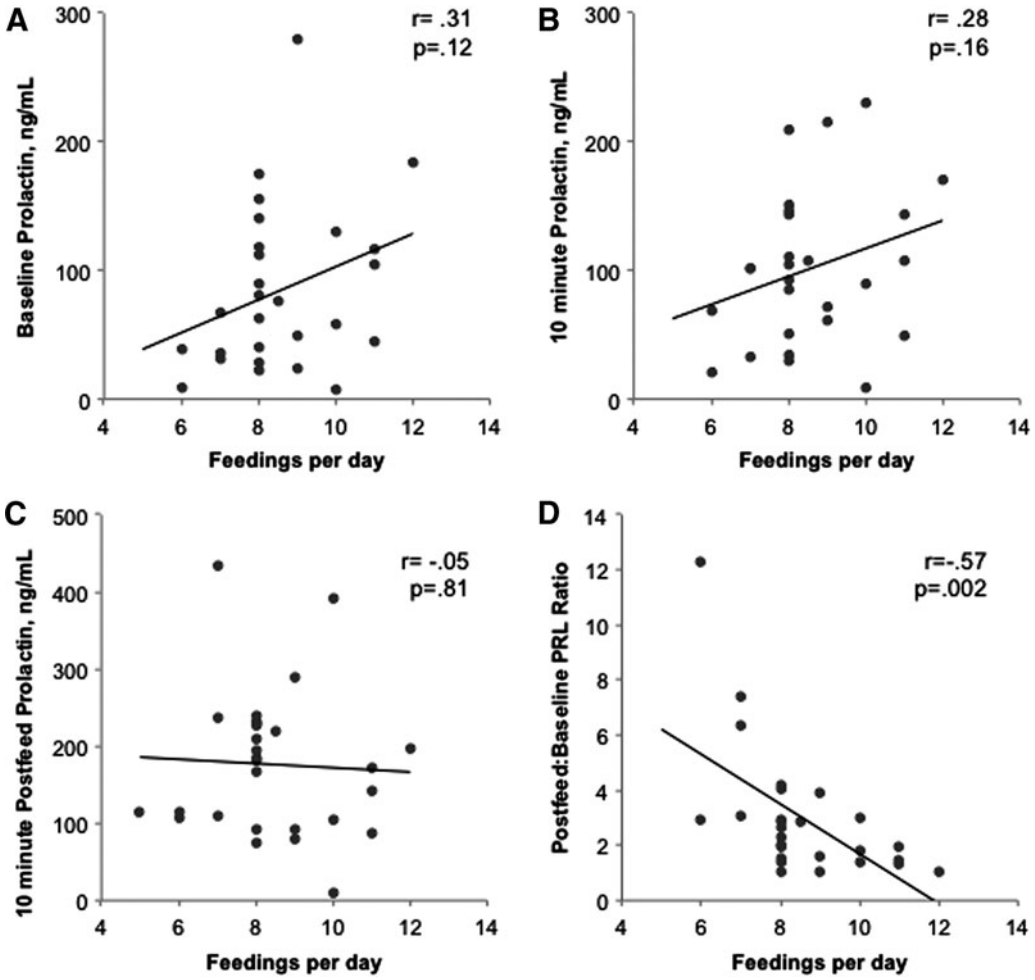

FIG. 2. Correlation between number of breastfeedings per day and prolactin levels at **(A)** baseline, **(B)** 10 minutes after starting feeding, and **(C)** 10 minutes after the end of feeding and **(D)** the ratio of postfeeding:baseline prolactin levels among 28 exclusively breastfeeding women at 8 weeks postpartum.

feeding frequency at 8 weeks. This association may reflect higher baseline prolactin values among women who feed more frequently or may result from a need to feed more frequently to allow adequate milk transfer in the setting of lower prolactin response. In either case, our results suggest that the normal range for ratio of postfeeding:baseline prolactin levels may vary, depending on feeding frequency. The wide variations that we observed in our sample, as well as the lack of evidence for an association between prolactin and milk production, suggest that clinically useful reference values for prolactin during lactation may not exist.

Our findings must be interpreted in the context of the study design. Our study population was largely white, highly educated, and oversampled for women with a history of depression or anxiety. Thus our results may not be generalizable to other populations. However, we did not detect an association between maternal mood history, state anxiety, or antidepressant use and endocrine values, suggesting that inclusion of these participants did not bias our results. The timing of our sample collection is an important limitation. Noel et al.[29] found that the prolactin level peaks 40 minutes after the baby is put to the breast. We sampled prolactin at baseline, 10 minutes of feeding, and 10 minutes after feeding, and differences in the time from initiation of feeding to sample collection may have increased the variability in our results. Moreover, prior work suggests that one-third of women achieve peak prolactin levels at 1 hour or more after feeding,[14] so it is possible that we underestimated peak postfeeding prolactin levels. However, in clinical practice, multiple samples are not practical, whereas a sample collected 10 minutes after feeding is feasible to achieve. In addition, we did not measure milk transferred during feeding in our study, limiting our ability to interpret associations between feeding frequency and endocrine profiles.

Conclusions

We found significant changes in prolactin and thyroid profiles among exclusively breastfeeding women during the first 8 weeks postpartum. We further found that a wide range of prolactin levels was compatible with exclusive breastfeeding. Our results underscore the need for longitudinal research to define reference values for prolactin and thyroid levels in the postpartum period. These studies should also evaluate the clinical utility of checking prolactin levels in mothers with low milk supply. Such work will provide

evidence to improve clinical evaluation and management of women with milk supply concerns.

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Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Alison M. Stuebe, MD, MSc
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
University of North Carolina School of Medicine
3010 Old Clinic Building, CB 7516
Chapel Hill, NC 27599

E-mail: astuebe@med.unc.edu